REMARKS

Applicants respectfully request entry of the present Amendment to facilitate prosecution and place the claims in condition for allowance.

After entry of the present amendment, claims 4, 5, 7, 9, 10, 13, 16, 18-21, 23-29, 31-39, 53-56, 59, 98, 99, 102, 103, 117 and 120 are pending.

Support for Amendments

Support for the amendments above is found in the specification as discussed below. No new matter has been added.

Claims 1 and 119 have been cancelled and rewritten as new claim 120 in part due to the square brackets present in the claims. The use of these brackets is based on standard peptide nomenclature, as employed by those skilled in the art. Accordingly, Claim 1 was rewritten to avoid confusion regarding what has been amended in the claim, since 37 CFR § 1.121 requires the changes be shown by brackets. The compounds of claim 120, which are summarized in Chart 1 below, do not represent new subject matter. The original claims as filed recited methods drawn to particular uses of MSH analog compounds. This recitation, read in light of the specification, includes all the compounds one skilled in the art would understand from reading the disclosure. The compounds of claim 120 are fully supported by the original specification as filed.

The following changes were made in rewriting amended claim 1 as new claim 120: (1) correction of typographical errors enumerated at pages 2-3 of the Office Action, (2) adoption of the Examiner's suggestions for claim amendments to obviate the rejection under 35 USC § 112, second paragraph of claim 1 at pages 2-3 of the Office Action, and (3) combining the α-MSH analog compounds of former claim 119. Explicit support for the α-MSH analog compounds of former claim 119, which are now incorporated into new claim 120 solely to facilitate prosecution of the instant amendment, is found in the specification, for example at page 43, line 9 – page 45, line 11. Support for correction of typographical errors is self-evident.

Claims 4, 7, 18, 31, 39 and 59 have been amended to clarify the invention, correct claim dependencies and follow the Examiner's suggestions for claim amendments to obviate

the rejection under 35 USC § 112, second paragraph of claim 1 at pages 2-3 of the Office Action. Claims 5, 10, 13, 16, 18-21, 23-29, 31-36, 53-56, 98, 102 and 117 have been amended to correct claim dependencies in light of the present amendment canceling claim 1 and introducing new claim 120. Support for these corrections is self-evident.

REJECTIONS UNDER 35 U.S.C. § 102(b)

Claims 1, 4, 5, 7, 9, 10, 19-21, 23-27, 31, 53, 59, 98 and 99 stand rejected as being **anticipated** under 35 U.S.C. § 102(b) by Girten et al. (U.S. Patent No. 5,726,156) ("Girten") and Mountjoy et al. (Mol. Cell. Endocrinol. 128, 171-177 [1997]) ("Mountjoy"). The Office Action provides nine anticipation rejections which are enumerated individually below.

With respect to each rejection, Applicants respectfully disagree and maintain that the methods of administering Cytokine Regulatory Agents of Girten do not anticipate the methods of administering α-MSH analog compounds of the present invention because the **chemical structures** of the compounds disclosed in Girten are **not identical** to those of the compounds administered in the methods of the present invention. Applicants assert that one skilled in the art could read claim 1 (now withdrawn) and understand that the methods disclosed in Girten do not anticipate the methods of former claim 1.

Notwithstanding, to facilitate prosecution and clarify some aspects of the invention, Applicants have added new claim 120, which represents a rewritten version of claim 1, wherein certain α-MSH analog compounds described in the specification (for example at pages 43-47) are claimed. The compounds of claim 120 are not new matter.

1. ***To anticipate, the X_1, X_2 and X_3 moieties of the Girten compounds must describe one or more of the 4, 5 and 10 positions in the α-MSH analogues administered in the methods of the present invention.***

In the present invention, a standard amino acid nomenclature is used which refers to the position of amino acid in the 13 amino acid chain sequence of human α-MSH (SEQ ID NO:2).[1] As known in the art, substitutions in this sequence can be designated in a

[1] Human α-MSH has the following amino acid sequence: Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val.

conventional "short-hand" by appropriately using square brackets and superscripts to indicate substitutions and subscripts after the name of the sequence to indicate truncation of the sequence, as follows: [Cys^4]-α-MSH_{4-10} means "amino acids 4-10 of human α-MSH with Cysteine substituted at the 4-position," or Cys-Glu-His-Phe-Arg-Trp-Gly.

For ease of discussion, Applicants provide the following table to indicate the structures that are claimed in claim 120 as Chart 1 below. In Chart 1, the first row provides the sequence of human a-MSH amino acid residues as a basis for comparison, and the remaining rows each indicate the compounds recited by individual subparts (a) – (k) of claim 120. The nomenclature in the chart follows standard naming of amino acid compounds in the art, or abbreviations for language recited in claim 120. Residues indicated in bold type indicate residues that differ from the human-type α-MSH, which is provided for reference in the first row of the chart.

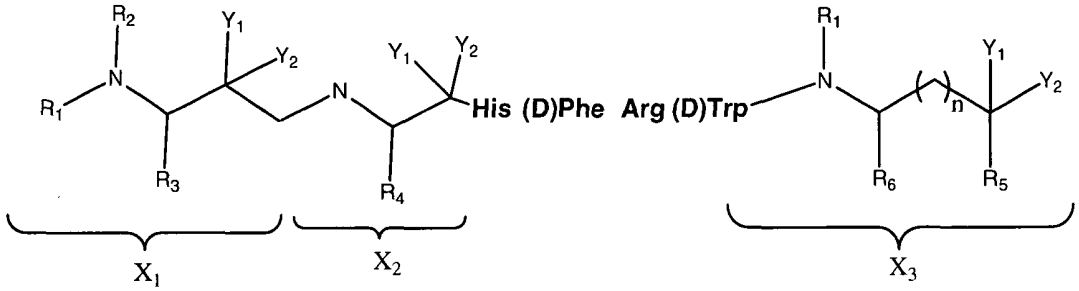
Chart 1: Comparison of human α-MSH residue sequence and α-MSH analogue compound residue sequences of claim 120[2]

Human MSH	Ac-*Ser*	*Tyr*	*Ser*	*Met*	*Glu*	*His*	*Phe*	*Arg*	*Trp*	*Gly*	*Lys*	*Pro*	*Val*-NH_2
Claim 120 (a)	Ac-Ser	Tyr	Ser	**Cys**	Glu	His	**D-Phe**	Arg	Trp	**Cys**	Lys	Pro	Val-NH_2
(b)	Ac-Ser	Tyr	Ser	**Nle**	**X5 =** Glu or **Asp**	His	**X7 =** Phe or **D-Phe**	Arg	Trp	**X10 = dbaa, Lys, orn, dab,** or **dpr**	Lys	Pro	Val-NH_2
(c)	Ac-Ser	Tyr	Ser	**Cys**	Glu	His	Phe	Arg	Trp	**Cys**	Lys	Pro	Val-NH_2

[2] Regarding **Chart Nomenclature**: "Ac" indicates the Amino-terminal residue of a claimed sequence; "-NH_2" indicates the Carboxyl-terminal residue of a claimed sequence. The compounds of claim 120(b) include all compounds where X5, X7 and X10 are independently varied. The nomenclature of residues corresponding to X10 in claim 120(b) corresponds to the recitation of "$X_{aa}{}^{10}$ is a dibasic amino acid ["dbaa"], Lys, ornithine ["orn"], 2,4-diaminobutyric acid ["dab"], or 2,3 diaminopropionic acid (Dpr)." The compounds of 120(d), include all compounds formed by independently varying the R1, W, X, Y, Z and R2 residues. For example, 120(d) compounds include: Ac-Gly-His-Phe-Arg-Try-NH_2, Ac-Met-Glu-His-Phe-Arg-Trp-NH_2 and Ac-Gly-His-Phe-Arg-Trp-Gly-NH_2, etc. In like fashion, the compounds of claim 120(k) include all compounds where AA5 and AA10 are independently varied. The nomenclature corresponding to AA5 and AA11 in claim 120(k) corresponds to the recitation of "AA^5 [or AA^{11}] may be either a L-or D-amino acid having an omega amino or carboxyl group in the side chain."

(d)				Ac-**R1**		**W**	**X**	**Y**	**Z**	**R2**-NH_2			
				R1 = **Gly**, **Met**-Glu-, **Nle**-Glu-, or **Tyr**-Glu-		W = His or **D-His**	X= Phe, **D-Phe**, **Tyr**, **D-Tyr**, or **pNO$_2$-D-Phe**	Y= Arg or **D-Arg**	Z = Trp or **D-Trp**	R2 = -NH_2, Gly, or Gly-Lys			
(e)	Ac-Ser	Tyr	Ser	Met	Glu	His	**D-Phe**	Arg	Trp	Gly	Lys	Pro	Val-NH_2
(f)	Ac-Ser	Tyr	Ser	**Nle**	Glu	His	**D-Phe**	Arg	Trp	Gly	Lys	Pro	Val-NH_2
(g)				Ac-**Nle**	Glu	His	**D-Phe**	Arg	Trp	Gly-NH_2			
(h)				Ac-**Nle**	Glu	His	**D-Phe**	Arg	Trp	Gly	Lys-NH_2		
(i)				Ac-**Nle**	Glu	His	**D-Phe**	Arg	**D-Trp**	Gly	Lys-NH_2		
(j)				Ac-**Nle**	Glu	His	**D-Phe**	Arg	Trp-NH_2				
(k)	Ac- or Ac-Ser-Tyr-Ser			**Nle**	**AA5** (see **FN2**)	His	**D-Phe**	Arg	Trp	**AA10** (see **FN 2**)	-NH_2, Lys-NH_2, Lys-Pro-NH_2, or Lys-Pro-Val-NH_2		
	Ac- or Ac-Ser-Tyr-Ser			**Nle**	**AA5** (see **FN2**)	His	**D-Phe**	Arg	Trp	**Gly**	**AA11** (see **FN 2**	-NH_2, Lys-NH_2, Lys-Pro-NH_2, or Lys-Pro-Val-NH_2	

In contrast, the compounds taught by Girten are expressed in a nomenclature that is a combination of both chemical structural formulae and amino acid nomenclature. Specifically, Girten teaches structures of the formula X_1-X_2-His-(D)Phe-Arg-(D)Trp-X_3 disclosed from col. 3, line 34 to col. 4, line 64. This structure is shown below:



The "His-(D)Phe-Arg-(D)Trp" portion of this structural formula forms an invariant amino acid sequence "core" of the Girten compounds. The X_1, X_2 and X_3 moieties of the Girten compounds can, themselves, be varied by the substituents Y_1, Y_2 and $R_{1\text{-}6}$ as shown above. *See* col. 3, lines 35-66 *et seq.*

The nomenclature of Girten can be compared to the compounds of the present invention in the following manner. Where Y_1 and Y_2 of Girten together form a carbonyl (col. 3, lines 57-58), and R_1 and R_2 are hydrogen (col. 3, lines 57-58 and line 60), then X_1, X_2 and X_3 are analogous to amino acid positions 4, 5 and 10 respectively in human α-MSH. However, Girten fails to teach specific side chains of the α-carbons of the X_1-X_3 residues which would result in compounds that anticipate the present invention.

2. ***The Cytokine Regulatory Agents of Girten are not identical to the chemical structures of the compounds administered in the methods of instant invention.***

To anticipate the methods of the instant invention, Girten must disclose one or more methods *identical* to methods of the instant invention. Specifically, to anticipate, Girten must teach a method for the administration of one or more of the α-MSH analog compounds of the present invention in a method of decreasing body weight or reducing weight gain. Applicants respectfully assert that this is not the case because Girten does not disclose methods of administering a compound of any **chemical structures** that are identical to those administered in the methods of the present invention.

As noted above, Girten teaches structures of encompassed by the formula X_1-X_2-His-(D)Phe-Arg-(D)Trp-X_3 disclosed from col. 3, line 34 to col. 4, line 64. Applicants assert that given the scope of the X_1, X_2 and X_3 moieties, Girten fails to disclose *any* of the compounds claimed in the methods of the instant invention, as demonstrated below.

a. *The α-MSH analog compound of claim 120(a) is not disclosed by Girten.*

Girten provides that in X_1, the R_3 moiety must be "a linear or branched alkyl group having 1-6 carbon atoms." Girten at col. 3, lines 61-63. In direct contrast, the compound of 120(a) has a Cys^4 substitution at the 4 position of α-MSH, which would correspond to the X_1 moiety in the Girten formula. The Cys amino acid has a $-CH_2S$ side chain in what would correspond to R_3 of the Girten X_1 moiety. Since Girten is restricted to an alkyl chain at this position and does not allow for a sulfur-containing group at R_3, Girten *cannot* anticipate a $-CH_2S$ side chain at R_3 of the Girten X_1 moiety. Similarly, the [Cys^{10}] α-MSH substitution also present in the compound of claim 120(a) is also incompatible with the R_6 group in the

X_3 portion of Girten. Girten does not disclose the compounds of claim 120. Accordingly, Girten cannot anticipate method of claim 120(a).

b. *The α-MSH analog compound of claim 120(**b**) is not disclosed by Girten.*

Girten provides that in X_2, the R_4 moiety must be one of several specified *nitrogen-containing* chemical structures.[3] Girten at col. 3, lines 63-64. In direct contrast, the compound of 120(b) has a Glu^4 or an Asp^4 substitution at the 5 position of α-MSH, which correspond to the X_2 moiety in the Girten formula. The Glu amino acid has a $-CH_2\ CH_2OO$ side chain in what would correspond to moiety R_4 of the Girten X_2 moiety. Since $-CH_2\ CH_2OO$ does *not* contain nitrogen, it cannot be described by the X_2 moiety in the Girten formula. Likewise, the Asp amino acid has a $-CH_2OO$ side chain in what would correspond to moieties R_4 of the Girten X_2 moiety. Since $-CH_2OO$ does *not* contain nitrogen, it too cannot be described by the X_2 moiety in the Girten formula. Similarly, the various substitutions at the 10 position of α-MSH nt in the compound of claim 120(b) are also incompatible with the R_6 group in the X_3 portion of Girten.

Girten does not disclose the compounds of claim 120. Accordingly, Girten cannot anticipate the method of claim 120(b).

c. *The α-MSH analog compound of claim 120(**c**) is not disclosed by Girten, for the same reasons discussed above for the compound of claim 120(a).*

Briefly, the compound of 120(c) also has a Cys^4 substitution at the 4 position of α-MSH, which would correspond to the X_1 moiety in the Girten formula. The Cys amino acid has a $-CH_2S$ side chain in what would correspond to moieties R_3 of the Girten X_1 moiety. Since $-CH_3S$ contains sulfur, it is not an alkyl group. Similarly, the $[Cys^{10}]$ α-MSH substitution also present in the compound of claim 120(c) is also incompatible with the R_6 group in the X_3 portion of Girten. Girten does not disclose the compounds of claim 120. Accordingly, Girten cannot anticipate the method of claim 120(c).

[3] The R_4 structures of Girten are selected from the group consisting of $(CH_2)_m$-$CONH_2$, $(CH_2)_m$-$CONHHR_1$, and $(CH_2)_m$-CONHA (*bold added for* emphasis to indicate the requisite presence of nitrogen in all of these compounds), where A, R_1 and m are defined at col. 3, line 58 et seq.

d. *The α-MSH analog compound of claim 120(d) is not disclosed by Girten.*

The compounds of 120(d) are described by the formula "R_1-W-X-Y-Z-R_2." If W-X-Y and Z are His, (D)-Phe, Arg and (D)Trp so as to match the invariant "backbone" of Girten, none of the compounds of claim 120(d) are anticipated by the Girten compounds. For Girten to anticipate, the X_2 moiety of Girten must describe the Gly or Glu amino acid sequences in the R_1 formula of claim 120(d). Gly has a hydrogen side chain and Glu has a sidechain with the structure: $-CH_2-CH_2-CONH_2$. Accordingly, for Girten to anticipate, the X_2 portion of the R_4 moiety of Girten must be *either* hydrogen (to anticipate the Gly amino acid in position R_1 of the formula of claim 120(d)) *or* describe the glutamine side chain structure (ie, $-CH_2-CH_2-CONH_2$).

Instead, Girten provides that in X_2, the R_4 moiety must be one of several specified *nitrogen-containing* chemical structures. Girten at col. 3, lines 63-64. Neither Glu or Gly contains nitrogen in the sidechain portion of their amino acid structure, which corresponds to the X_2 portion of the R_4 moiety of Girten.

Girten does not disclose the compounds of claim 120. Accordingly, Girten cannot anticipate the method of claim 120(d).

e. *The α-MSH analog compound of* claims 120(**e**), 120(**f**), 120(**g**), 120(**h**), 120(**i**) **and** 120(**j**) are not disclosed by Girten.

Girten provides that in X_2, the R_4 moiety must be one of several specified *nitrogen-containing* chemical structures.[4] Girten at col. 3, lines 63-64. In direct contrast, the compounds of 120(e) – 120(j) *all* include a glutamate (Glu or E) amino acid residue at the 5 position of α-MSH (i.e., the *absence* of substitution at the 5 position of an unsubstituted human α-MSH, SEQ ID NO:2, indicates the presence of Glu at the 5 position because there is no substitution to the contrary). The Glu residue in each compound of claim 120(e) – 120(j) corresponds to the X_2 moiety in the Girten formula. The Glu amino acid has a $-CH_2CH_2OO$ side chain in what would correspond to moiety R_4 of the Girten X_2 moiety. Since $-CH_2CH_2OO$ does *not* contain nitrogen, it cannot be described by the X_2 moiety in the Girten formula.

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[4] The R_4 structures of Girten are selected from the group consisting of $(CH_2)_m$-$CONH_2$, $(CH_2)_m$-$CONHHR_1$, and $(CH_2)_m$-CONHA (bold added for emphasis to indicate the requisite presence of nitrogen in all of these compounds), where A, R_1 and m are defined at col. 3, line 58 et seq.

Girten does not disclose the compounds of claim 120. Accordingly, Girten cannot anticipate methods of claim 120(e), 120(f), 120(g), 120(h), 120(i) or 120(j).

f. *The α-MSH analog compounds of* claims 120(**k**) are not disclosed by Girten.

The compounds of 120(k) are described by several substitutions of various truncations of the human α-MSH, including of an "AA^{10}" moiety at the 10 position or an "AA^{11}" at the 11 position of the α-MSH analog. The AA^{10} moiety is selected from a variety of amino acids or amino acid analogs that have either carboxyl-terminated side chains (i.e., Asp, Glu, α,β-aminoadipic acid, α–aminopimelic acid or higher homologues thereof)[5] or amino terminated (diaminopropionic acid, α,β–diaminobutyric acid, Orn, Lys)[6] side chains.

The AA^{10} substitution in the compounds of claim 120(k) corresponds to the X_3 moiety of Girten. Girten provides that in X_3, the R_6 moiety must be H or "a linear or branched **alkyl** group having 1 to 6 carbon atoms, or a cyclic alkyl group having 3 to 6 carbon atoms." Girten at col. 3, lines 61-65. Accordingly, Girten does not describe any of the AA^{10} moieties among the structures for the the R_6 moiety. Girten cannot disclose the α-MSH analog compound of claim 120(k).

Other compounds of claim 120(k) comprise an AA^{11} moiety. Since the Girten structure *terminates* in X3, Girten has no corresponding structure to compare with the AA^{11} moiety of the instant invention. Girten does not anticipate the methods recited in claim 120(k) where the AA^{11} substitution is made.

Girten does not disclose the compounds of claim 120. Accordingly, Girten does not anticipate the methods of claim 120(k).

3. All anticipation rejections are inapposite in light of the argument above because the Cytokine Regulatory Agents of Girten do not anticipate the structures of the instant invention.

The Office Action provided rejections of the claims under 35 USC § 102(b) for being anticipated by the Girten and Mountjoy references. Applicants respectfully submit that in

[5] These compounds have the general side chain formula of: $--(CH_2)_nNH_2$ where n is an integer.
[6] These compounds have the general side chain formula of: $--(CH_2)_nCOO$ where n is an integer.

light of the discussion above, or at least in light of the amendments made herein to the claims, that the various bases for these rejections have been obviated.

Specifically, the Office Action made the following rejections of under 35 USC § 102(b):

a. The methods of claims 1, 4, 7 and 9 are rejected in view of column 28, Example XX, column 16, Example II and therapeutic compositions at column 7, line 64 – column 8, line 17 of Girten. Office Action at 3.

b. Claim 10 is rejected in view of Mountjoy because "the α-MSH compound in the method of claim 1 inherently has the identifying characteristics recited in claim 10, i.e., ability to bind MCR expressed in peripheral tissues and stimulating lipolysis because these properties of α-MSH were known in the prior art (for example, Mountjoy et al., page 173, first full paragraph; page 175 at 3)." Office Action at 3-4.

c. Claims 19-21 and 23 are rejected as anticipated by Girten because "Girten et al. disclose transdermal, topical, parenteral and controlled release (skin patch) administration of the a-MSH analog of claim 1 (column 13, lines 28-42)." Office Action at 4.

d. Claim 24 is rejected as anticipated by Girten because "Girten et al. disclose that administration of the α-MSH analog of claim 1 was insufficient to cause a statistically significant change in the appetite of the animal as compared to before administration of the analog (column 29, lines 53-55)." Office Action at 4.

e. Claims 25-27 stand rejected as anticipated by Girten because "Girten et al. disclose administration of the α-MSH analog of claim 1 in ranged amounts overlapping those of the claims (column 14, lines 7-12; about 0.0001 to 0.5 or [sic.] to 100 mg/kg body weight depending on route of administration; column 28, Example XX)." Office Action at 4.

f. Claim 31 stands rejected as anticipated by Girten because "Girten et al. disclose that the decrease in body weight can be measured within at least about one week of administration of the a-MSH analog (column 28, lines 49-55)." Office Action at 4.

g. Claim 53 stands rejected as anticipated by Girten because "Girten et al. disclose the method of claim 1 wherein the animal is a human (column 2, line 65 – column 3, line 1; column 9, lines 31-35).

h. Claim 59 stands rejected as anticipated by Girten at column 28, Example XX "wherein binding of α-MSH agonists to melanocortin receptors was known in the prior art (for example, Mountjoy et al, abstract)." Office Action at 4.

i. Claims 98 and 99 stand rejected as anticipated by Girten because "Girten et al. disclose the method of claim 1 wherein the animal is at risk for or suffering from an obesity associated disorder including NIDDM (column

11, lines 49-63) and cardiovascular disease (column 12, lines 10-20)." Office Action at 4.

Applicants respectfully submit that the discussion and amendments above are fully responsive to each and every rejection detailed above. Specifically, Applicants assert that if the compounds used in the methods of the present invention are not disclosed by Girten (as discussed above), then Girten cannot anticipate any of the methods of the present invention.

REJECTIONS UNDER 35 U.S.C. § 103(a)

Various claims stand rejected under 35 USC § 103(a) for being obvious in light of Girten, Mountjoy and Hadley et al. (U.S. Patent No. 5,731,408) ("Hadley"), Hruby et al. (U.S. Patent No. 4,485,039) ("Hruby I") and Hruby et al. (U.S. Patent No. 5,714,576) ("Hruby II"), and various combinations thereof, as detailed below.

Every one of these rejections is based on the Girten reference, either alone or in combination with other references. Applicants respectfully traverse all of these rejections, asserting that the Office Action mischaracterizes how Girten would be read by one of ordinary skill in the art at the time of the present invention. There is not teaching in Girten or in the art that would motivate one skilled in the art to modify the compounds of Girten to administer the α-MSH or α-MSH analog compounds in accordance with the methods of the present invention.

As discussed above, Girten teaches structures of the formula X_1-X_2-His-(D)Phe-Arg-(D)Trp-X_3, where X_1, X_2 and X_3 are chemical structures disclosed from col. 3, line 34 to col. 4, line 64. Based on the structural analysis above, it is self-evident that the compounds of Girten do not teach SEQ ID NO:1,[7] SEQ ID NO:2[8] or any α-MSH analog compound[9] of the present invention. In contrast to the scope of the structures taught by Girten, the Office Action characterizes the Girten reference as:

1. depending on "known functions" of MSH (with respect to claim 13);

[7] Briefly, as discussed above, Girten does not teach SEQ ID NO:1 of the instant invention because the Glu amino acid in SEQ ID NO:1 corresponds to the X_2 position in the Girten formula, and the definition of X_2 taught by Girten cannot structurally include a Glu amino acid residue.

[8] As discussed above, Girten does not teach SEQ ID NO:2 of the instant invention because of the Glu at the 5 position, as well as the Met at the 4 position of α-MSH.

[9] *See* detailed discussion above regarding the α-MSH analog compounds of claim 120

2. providing MSH compounds, and therapeutic compositions thereof, to provide a "weight reducing method" (rejections of claims 16 and 18, claims 54-56; claims 28, 29 and 32-35; claims 36-39; and claims 102-103); and
3. providing a "cyclic α-MSH analog peptide which can be produced by inducing the formation of a covalent bond between two reactive amino acid side chains..." (rejection of former claim 119).

Applicants disagree with these characterizations of the compounds taught by Girten; Girten does not teach "MSH compounds," as understood by the present invention. As discussed above, the formula defining the compounds of Girten does not teach the α-MSH, or α-MSH analog compounds of the present invention.

More specifically, the Office Action makes the following assertions with respect to claims 13, 16, 18, 28, 29, 32-35, 36-39, 54-56, 102-103, 119:

1. The claim 13 embodiment of the claim 1 method differs from the method of Girten et al. wherein the MSH compound is α-MSH. However, it would have been obvious and the skilled practitioner in the art would have been motivated at the time the claimed invention was made to use the native MSH compound for the obvious benefit of convenience in obviating chemical synthesis of analogs and in view of its known functions on which the Girten et al. method depends.
2. The embodiments of the claim 1 method in claims 16 and 18 differ from the Girten et al. method wherein the MSH compound binds with higher affinity to a receptor in peripheral tissues than it does to MC4-R receptors and wherein the compound does not activate MC4-R. However, Mountjoy et al. teach that MC4-R receptors occur primarily in the brain (page 172, column 2, lines 5-7) rather than in peripheral tissues whereas a different receptor, MC5-R, occurs in adipocytes and other peripheral tissues (page 172, Table 1; page 175 at 3.). Therefore, it would have been obvious and the skilled practitioner in the art would have been motivated at the time the claimed invention was made to improve on the weight-reducing method of Girten et al. by making it more specific for fat loss via directing the MSH compound to receptors in adipose tissue while minimizing side effects of binding to MC4-R receptors in the brain.
3. Regarding claims 54-56, the method of Girten et al. differs from that of claim 1 wherein the therapeutic composition further comprises an antagonist of MC4-R or an agent that inhibits binding of the MSH compound to MC4-R or inhibits it from entering the central nervous system. However, Hadley et al. teach antagonists of MC4-R which may be used to block the physiological response of cells to α-MSH (column 6, Table III; lines 48-50). It would have been obvious and the skilled practitioner in the art would have been motivated at the time the claimed invention was made to improve on the weight-reducing method of Girten et al. by making it more specific for fat loss by including with the α-MSH compound an

antagonist of MC4-R or an agent that inhibits binding of the MSH compound to MC4-R or inhibits it from entering the central nervous system such as the peptides taught by Hadley et al. for the obvious benefit of by making the method more specific for fat loss via minimizing binding to MC4-R receptors in the central nervous system.

4. Claims 28, 29 and 32-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Girten et al. (56,726, 156) as applied to claim 1 above and further in view of routine art practice. The claimed embodiments of the claim 1 method differ from the Girten et al. method wherein ranges for the concentration of the MSH compound in the therapeutic composition are specified whereas the reference provides the dose ranges of the MSH compound (column 14, lines 7-12). However, in view of routine practice in the art and absent unexpected results, it would have been obvious and the skilled practitioner in the art would have been motivated at the time the claimed invention was made to determine the concentration of the MSH compound in the composition based on experimental parameters and expected results. In *In re Aller*, 105 USPQ 233, the court found that changes of an old process within the broad teaching of the prior art does not impart patentability in the absence of unexpected results.

5. The embodiments of the claim 1 method of claims 32-34 differ from the method of Girten et al. wherein serum MSH and leptin levels and ration are measured prior to administration of the MSH compound. However, in view of routine practice in the art and absent unexpected results, it would have been obvious and the skilled practitioner in the art would have been motivated at the time the claimed invention was made to determine the levels and ration of MSH and leptin in serum prior to therapy for the obvious benefit of obtaining a baseline measurement from which to determine appropriate therapeutic amounts of the MSH compound to be administered and from which to measure serum levels of administered compound in view of the know role of leptin in weight loss. In *In re Aller*, 105 USPQ 233, the court found that changes of an old process within the broad teaching of the prior art does not impart patentability in the absence of unexpected results.

6. Regarding claim 35, it would have been further obvious in view of art practice and one of ordinary skill in the art at the time the claimed invention was made would have been motiviated to determine the BMI of an individual for the obvious benefit of establishing a baseline weight prior to treatment from which to measure weight loss.

7. Claims 36-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Girten et al. (56,726,156) as applied to claim 1 above, and further in view of Mountjoy et al. 1997 (Mol. Cell. Endocrinol. 128:171-177). The embodiments of claims 36-39 of the method of claim 1 differ from the method of Girten et al. wherein the therapeutic composition further comprises another body weight regulating agent; wherein the agent is leptin; wherein the ration of MSH compound to leptin is about 1:100; and wherein the leptin dose is about 0.1 μg to about 100 mg per kg body weight of the animal. However, Mountjoy et al. teach that leptin is produced by fat and when administered to mice causes them to lose

weight by decreasing their food intake (page 174 at 7., lines 6-9). It would have been obvious and the skilled practitioner in the art would have been motivated at the time the claimed invention was made to add another body weight regulating agent, especially leptin, to the MSH compound administered in the method of Girten et al. in view of the further teaching of Mountjoy et al. that α-MSH increases lipolysis and may regulate leptin production indirectly by decreasing adipose tissue mass (page 174, column 2, lines 15-19) for the obvious benefit of increasing the potential for weight loss via fat reduction.

8. Claims 102 and 103 are rejected under 35 U.S.C. 103(a) as being unpatentable over Girten et al. (56,726,156) as applied to claim 1 above, and further in view of scientific reasoning. The claim 102-103 embodiments of the claim 1 therapeutic method differ from the method of Girten et al. wherein the body weight to be decreased is a side effect resulting from administration of a pharmaceutical compund wherein the pharmaceutical compound is selected from valproic acid, lithium et al.. However, absent evidence to the contrary, it would have been known to the skilled practitioner in the art at the time the claimed invention was made that the cause of the body weight to be reduced was immaterial to the practice of the claimed invention therapeutic method. Therefore, the Girten et al. method would have been the same as the method of claim 1 in the embodiments of claims 102 and 103.

9. Claim 119 is rejected under 35 U.S.C. 103(a) as being unpatentable over Girten et al. (56,726,156) as applied to claim 1 Above, and further in view of Hruby et al. (4,485,039 and 5,714,576).

10. It would have been obvious and the skilled practitioner in the art would have been motivated at the time the claimed invention was made to substitute an α-MSH analog peptide such as the Ac-[Cys^4, D-Phe^7, Cys^{10}] α-MSH analog of Hruby '576 for the α-MSH analog in the therapeutic method of Girten et al. in view of the teaching of Girten et al. that "a cyclic peptide may provide...increased stability, increased solubility, decreased immunogenicity or decreased clearance in vivo" (column 7, lines 51-54) and the teaching of Hruby et al. '039 that α-MSH has an extremely short half-life in serum whereas the α-MSH analogs having Cys^4 and Cys^{10} substitutions and connected by a covalent bond exhibit prolonged biological activity and greater resistance to enzymatic degradation than the native peptide (column 2, lines 57-64; column 3, lines 18-24) as well as the teaching of Hruby et al. '576 that substitution of D-Phe for Phe at position 7 of the Hruby et al. '039 peptide resulted in enhanced and prolonged activity (column 3, lines 1-3).

Applicants respectfully assert that each and every obviousness rejection made in the Office Action under 35 U.S.C. § 103(a), which are provided in detail above, are fully addressed and obviated by this Amendment. Applicants base this assertion on the chemical structure differences between the compounds taught by Girten and those of the present invention, as discussed above: namely, the chemical structure of the compounds taught by

Girten do not teach or suggest the compounds administered by the methods of the present invention.

Furthermore, there is no suggestion or motivation of record which demonstrate that a skilled artisan would combine the compounds taught by Girten with the Mountjoy, Hadley, Hruby I and Hruby II references in the manner asserted by the Office Action.

REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 1, 4, 5, 7, 9, 10, 13, 16, 18-21, 23-29, 31-39, 53-56, 59, 98, 99, 102, 103, 117 and 119 stand rejected under 35 U.S.C. § 112, second paragraph for being indefinite. With respect to each indefiniteness rejection, the Office Action suggests specific claim amendments. In addition to correction of typographical errors in claims 1, 4, 18, 31 and 39, the Office Action suggests deletion of the term "substantially" in claim 59 and an alternative manner of referring to amino acid sequences in claims 1, 7 and 9. Finally, the Office Action also asserts that claims 117 and 119 are indefinite because they contain non-elected subject matter and suggests that Applicants delete claim 117 and parts (b)-(k) of claim 119.

To facilitate prosecution and clarify the invention, Applicants have elected to adopt the suggestions of the Office Action, except for the suggestion to delete claim 117 and parts (b) – (k) of claim 119. Applicants have elected to delete claim 119 and combine claims 1 and 119 in new claim 120, without changing the content taken from claim 119 pertaining to methods of using certain α-MSH analogs. These particular α-MSH analogs of former claim 119, and new claim 120, are not new matter because they were known in the art at the time of the invention and the elected subject matter of the present invention pertains to, among other things, methods of using α-MSH analogs, as detailed in the specification and known in the art at the time of the invention. Accordingly, one skilled in the art at the time of the invention would have known of these compounds recited in former claim 119 and incorporated in new claim 120 as being α-MSH analogs. Claim 117 is made dependent on elected claim 120 and therefore now includes only elected subject matter.

Applicants believe that the bases for these rejections have been obviated in light of the amendments and discussion above.

CONCLUSION

Reconsideration and allowance of the pending claims in light of the amendments and remarks above is respectfully requested. Applicants respectfully submit that the present Amendment and Response places the pending claims in condition for allowance.

Respectfully Submitted,

S. Mrksich

K. Shannon Mrksich, Ph.D.
Registration No. 36,675
Attorney for Applicants

BRINKS HOFER GILSON & LIONE
P.O. Box 10395
CHICAGO, ILLINOIS 60610
(312) 321-4200

APPENDIX: Complete Listing of Pending Claims (37 CFR § 1.121)
Marked to Show Present Amendments

4. (Three Times Amended) The method of Claim [1]120, wherein said compound is selected from the group consisting of α-melanocyte stimulating hormone (α-MSH), a biologically active fragment of α-MSH, a homologue of α-MSH having α-MSH agonist[,] activity, [a non peptide mimetic of α-MSH having α-MSH agonist activity,] and a fusion protein comprising an α-MSH protein or a biologically active fragment thereof.

5. (Twice Amended) The method of Claim [1]120, wherein said compound is α-MSH.

7. (Once Amended) The method of Claim [1]120, wherein said compound is an analog of a peptide having [an]the amino acid sequence [represented herein by]of SEQ ID NO:2.

9. (Twice Amended) The method of Claim [1]120, wherein said compound is a peptide comprising [an]the amino acid sequence [represented herein by]of SEQ ID NO:1.

10. (Three Times Amended) The method of Claim [1]120, wherein said α-MSH compound has the following identifying characteristics: (1) an ability to bind to a melanocortin receptor that is expressed in peripheral tissues, and, (2) a biological activity selected from the group consisting of [S]stimulation of lipolysis and inhibition of the uptake of fatty acids by adipocytes.

13. (Twice Amended) The method of Claim [1]120, wherein said [C]compound binds to a melanocortin receptor expressed in the peripheral tissues with a higher affinity than to melanocortin-4 receptors (MC4-R).

16. (Once Amended) The method of Claim [1]120, wherein said compound does not bind to MC4-R under physiological conditions.

18. (Once Amended) The method of Claim [1]120, wherein said compound does not activate MC4-R [Linder]under physiological conditions.

19. (Once Amended) The method of Claim [1]120, wherein said therapeutic composition is administered transdermally.

20. (Once Amended) The method of Claim [1]120, wherein said therapeutic composition is administered topically.

21. (Once Amended) The method of Claim [1]120, wherein said therapeutic composition is administered parenterally.

23. (Once Amended) The method of Claim [1]120, wherein said therapeutic composition is administered in a controlled release formulation.

24. (Once Amended) The method of Claim [1]120, whereby administration of said compound is insufficient to cause a statistically significant change in the appetite of said animal as compared to before administration of said compound.

25. (Twice Amended) The method of Claim [1]120, wherein said composition is administered in a dose of from about 0.1 μg to about 10 mg per kg body weight of said animal.

26. (Twice Amended) The method of Claim [1]120, wherein said compound is administered in a dose of from about 1 μg to about 10 mg per kg body weight of said animal.

27. (Twice Amended) The method of Claim [1]120, wherein said compound is administered in a dose of from about 40 μg to about 1 mg per kg body weight of said animal.

28. (Once Amended) The method of Claim [1]120, wherein said compound is from about 0.1% to about 90% of said therapeutic composition by weight.

29. (Twice Amended) The method of Claim [1]120, wherein said [C]compound is from about 0.1% to about 1% of said therapeutic composition by weight.

31. (Twice Amended) The method of Claim [1]120, wherein said decrease in body weight in said animal [cart]can be measured within at least about one week of said step of administering said compound.

32. (Twice Amended) The method of Claim [1]120, wherein said animal has serum leptin levels between about 0 ng/ml and 50 ng/ml prior to said step of administration.

33. (Twice Amended) The method of Claim [1]120, wherein said animal has serum MSH levels between about 0 ng/ml and 10 ng/ml prior to said step of administration.

34. (Twice Amended) The method of Claim [1]120, wherein said animal has a ratio of serum MSH levels to serum leptin levels of greater than about 1:100 prior to said step of administration.

35. (Twice Amended) The method of Claim [1]120, wherein said animal is a human having a body mass index (BMI) of greater than 27 kilograms per square meter prior to administration of said compound.

36. (Twice Amended) The method of Claim [1]120, wherein said composition further comprises another body weight regulating agent.

37. (Once Amended) The method of Claim 36, wherein said another body weight regulating agent is leptin.

38. (Once Amended) The method of Claim 37, wherein said composition comprises a ratio of said MSH compound to leptin of about 1:100.

39. (Three Times Amended) The method of Claim 37, wherein said composition comprises[d] leptin in a dose of from about 0.1 [μpg]μg to about 100 mg per kg body weight of said animal.

53. (Once Amended) The method of Claim [1]120, wherein said animal is a human.

54. (Once Amended) The method of Claim [1]120, wherein said composition further comprises an antagonist of MC4-R.

55. (Three Times Amended) The method of Claim [1]120, wherein said composition further comprises an agent that inhibits binding of said α-MSH [C]compound to an MC4-R.

56. (Three Times Amended) The method of Claim [1]120, wherein said composition further comprises an agent which inhibits said α-MSH [C]compound from entering the central nervous system of said animal.

59. (Three Times Amended) A method of decreasing the body weight or reducing the rate of weight gain in an animal, comprising administering to an animal a melanocyte stimulating hormone (MSH) compound selected from the group consisting of α-MSH and an α-

MSH agonist in an amount effective to bind to melanocortin receptors expressed by said animal in said animal's peripheral tissues, said effective amount:

(a) being insufficient to [substantially]measurably change the appetite of said animal after said step of administering as compared to before said step of administering;

(b) being between about 0.1 μg and about 10 mg per kg[,] of body weight of said animal;

(c) being sufficient to affect a biological activity selected from the group consisting of:

(i) lipolysis; and[,]

(ii) uptake of fatty acids by adipocytes in said animal; and[,]

(d) being effective to measurably decrease the body weight or reduce the rate of weight gain of said animal after said compound has been administered to said animal.

98. (Twice Amended) The method of Claim [1]120, wherein said animal is at risk for or suffering from an obesity associated disorder.

99. (Reiterated) The method of Claim 98, wherein said obesity associated disorder is selected from the group consisting of non insulin dependent diabetes mellitus, cardiovascular disease, cancer, hypertension, osteoarthritis, stroke, respiratory problems, and gall bladder disease.

102. (Twice Amended) The method of Claim [1]120, wherein said animal is at risk [of]for or suffering from undesired body weight which is a side effect resulting from administration of a pharmaceutical compound.

103. (Reiterated) The method of Claim 102, wherein said pharmaceutical compound is selected from the group consisting of valproic acid, lithium, tricyclic antidepressants, and selective serotonin reuptake inhibitors (SSRI).

117. (Twice Amended) The method of claim [119]120, wherein [(k)] AA^5 is α,γ-diaminopropionic acid, α,γ-diaminobutyric acid, Orn, Lys, α,β-aminoadipic acid, α-aminopimelic acid, or higher homologs, Glu or Asp and AA^{11} is α,β-diaminopropionic acid, α,γ-diaminobutyric acid, Orn, Lys, α-aminoadipic acid, α-aminopimelic acid, Glu or Asp.

120. (New) A method to decrease the body weight or reduce the rate of weight gain in an animal, comprising administering to said animal a therapeutic composition comprising a melanocyte stimulating hormone (MSH) compound selected from the group consisting of α-MSH, α -MSH analog and a homologue of α-MSH having agonist activity;

wherein said therapeutic composition is administered to the periphery of said animal in an amount effective to measurably decrease body weight or reduce the rate of weight gain in said animal as compared to in the absence of administration of said compound; whereby administration of said compound minimizes delivery of said compound to the central nervous system of said animal;

wherein said α-MSH is a peptide comprising an amino acid sequence selected from the group consisting of: SEQ ID NO:1 and SEQ ID NO:2; and

wherein the α-MSH analog is selected from the group consisting of:

(j) Ac-[Cys^4, D-Phe^7, Cys^{10}] α-MSH, wherein said Cys residues are connected by a disulfide bond;

(k) Ac-[Nle^4, $X_{aa}{}^5$, His^6, $X_{aa}{}^7$, Arg^8, Trp^9, $X_{aa}{}^{10}$] NH_2, (SEQ ID NO:3)

wherein $X_{aa}{}^5$ is Glu or Asp, $X_{aa}{}^7$ is Phe or D-Phe and $X_{aa}{}^{10}$ is a dibasic amino acid, Lys, ornithine, 2,4-diaminobutyric acid, or 2,3 diaminopropionic acid (Dpr);

(l) IAc-[Cys^4, Cys^{10}]α-$MSH_{1-13}NH_2$;

(m) R_1-W-X-Y-Z-R_2,

wherein R_1 is selected from the group consisting of Ac-Gly-, Ac-Met-Glu-, Ac-Nle-Glu- and Ac-Tyr-Glu-;

W is selected from the group consisting of –His- and –D-His-;

X is selected from the group consisting of –Phe-, -D-Phe-, -Tyr, -D-Tyr-, (-pNO_2)D-Phe^7-;

Y is selected from the group consisting of –Arg- and –D-Arg-;

Z is selected from the group consisting of –Trp- and –D-Trp-; and,

R_2 is selected from the group consisting of $-NH_2$, -Gly-NH_2, and –Gly-Lys-NH_2;

(n) Ac-Ser-Tyr-Ser-M-Glu-His-D-Phe-Arg-Trp-Gly-Lys-Pro-Val-NH_2 (SEQ ID NO:4);

wherein M is selected from the group consisting of Met, Nle, and Cys;

(o) [Nle^4, D-Phe^7]-α-MSH;

(p) [Nle^4, D-Phe^7] –α-MSH_{4-10};

(q) [Nle^4, D-Phe^7] –α-MSH_{4-11};

(r) [Nle^4, D-Phe^7,D-Trp^9] –α-MSH_{4-11};

(j) [Nle^4, D-Phe^7] –α-MSH_{4-9}; and

(k) Ac-[Nle^4, AA^5, D-Phe^7, AA^{10}]-R_1 or Ac-[Nle^4, AA^5, D-Phe^7, AA^{11}]-R_2;

wherein AA^5 may be either a L-or D-amino acid having an omega amino or carboxyl group in the side chain;

wherein AA^{10} may be diaminopropionic acid, α,γ-diaminobutyric acid, Orn, Lys, α,β-aminoadipic acid, α-aminopimelic acid, or higher homologs, Glu or Asp;

wherein R_1 is the designation α-$MSH_{1-13}NH_2$, α-$MSH_{1-12}NH_2$, α-$MSH_{1-11}H_2$; α-$MSH_{4-13}NH_2$, or α-$MSH_{4-10}NH_2$;

wherein AA^{11} may be L- or D-amino acid having an omega amino or carboxyl group in the side chain;

wherein R_2 is the designation a $MSH_{1-13}NH_2$, α-$MSH_{1-12}NH_2$, α-$MSH_{1-11}NH_2$, α-$MSH_{4-13}NH_2$, or α-$MSH_{4-10}NH_2$.